REMARKS

Reconsideration of the present application in view of the following remarks is respectfully requested. Applicants note that the present amendment accompanies a Request for Continued Examination and is a submission under 37 C.F.R. § 1.114 that complies with 37 C.F.R. § 1.111. As set forth above, Applicants have hereby amended claims 42, 46, 47, and 51 for mere editorial purposes and not for reasons of patentability. No new matter has been added. Therefore, claims 42, 46-48, 51, and 57 are currently pending. Applicants note that these amendments are made without prejudice to the filing of any related divisional, continuation, or continuation-in-part application.

DRAWINGS

The Action objects to the drawings for the reasons cited in the Form PTO 948 attached to Paper No. 10. Applicants submit herewith 14 sheets of Replacement Drawings, Figures 1A– 19 for the Examiner's consideration.

REJECTION UNDER 35 U.S.C. § 101 (DOUBLE PATENTING)

In the Office Action mailed by the U.S. Patent and Trademark Office (hereinafter, "PTO") on December 2, 2002, claims 42, 46-48, 51 and 57 were provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 42, 46-48, 51 and 57 of co-pending U.S. Patent Application No. 09/185,904.

Applicants respectfully traverse this ground of rejection and submit that the pending claims of the two applications are drawn to patentably distinct subject matter. More specifically, Applicants note that the claims of the instant application recite that the presently claimed ANT polypeptide and fusion proteins are capable of localizing to a mitochondrial membrane, while pending claims 42, 46-48, 51 and 57 of co-pending U.S. Patent Application No. 09/185,904 do not include this feature. Accordingly, Applicants respectfully request that this provisional rejection be withdrawn.

Additionally, applicants wish to call the Examiner's attention to several related co-pending applications having claims potentially directed to similar subject matter. Reference to the "Table of Co-Pending Applications" appended hereto is therefore requested.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

In the Office Action, claims 42, 47, 51 and dependent claims were rejected under 35 U.S.C. §112, second paragraph, as indefinite. Specifically, it is alleged that there is insufficient antecedent basis for the acronym "ANT."

Applicants respectfully traverse this ground of rejection and respectfully submit that the claim term "ANT" is clearly defined in the claims and the specification, which has a meaning that is clear to a person skilled in the art (*see, e.g.,* page 1, lines 7-8; page 4, line 16; page 14, lines 17-18). Therefore, the recitation of "adenine nucleotide translocator" clearly provides antecedent basis for the acronym "ANT." Nevertheless, to expedite prosecution of the subject application, Applicants have amended claims 42, 46, 47, and 51 by defining the phrase "adenine nucleotide translocator" as equivalent to "ANT." Applicants respectfully submit that the scope of claims 42, 46, 47, and 51, as amended, is unchanged and sufficiently clear for a person having ordinary skill in the art.

Accordingly, Applicants respectfully submit that the claims satisfy the definiteness requirements of 35 U.S.C. §112, second paragraph and, therefore, request that this rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 102(b)

In the Office Action, claims 42 and 46 were rejected under 35 U.S.C. §102(b) as anticipated by Cozens *et al.* (*J. Mol. Biol. 206*:261-280, 1989). In particular, it is alleged that Cozens *et al.* disclose a human mitochondrial ADP/ATP translocase protein, or ANT protein, that is 100% identical to the amino acid sequence of SEQ ID NO:33. In addition, it is asserted that the Patent Office has a lesser burden of proof in making out a *prima facie* case of obviousness for product-by-process claims.

As an initial matter, Applicants respectfully submit that citation of the decisions *In re Fessmann* and *In re Marosi* in the Office Action (Paper No. 16, at page 4, last paragraph through page 5, top paragraph) is inapposite for the present rejection because these decisions are directed to the issue of obviousness under 35 U.S.C. § 103, and not to anticipation under 35 U.S.C. § 102.

Applicants respectfully traverse the rejection based on anticipation. In particular, Applicants submit that Cozens *et al.* fail to provide every element of the instant claims and, therefore, fail to anticipate the claimed invention. The present invention is directed, in pertinent part, to an isolated recombinant human adenine nucleotide translocator (ANT) polypeptide comprising an amino acid sequence that is at least 95 percent identical to a human ANT3 sequence as set forth in SEQ ID NO:33 and that is capable of binding an ANT ligand. In contrast, Cozens *et al.* fail to teach or suggest either an *isolated* or a *recombinant* human ANT polypeptide. Indeed, Cozens *et al.* fail to teach or suggest any human ANT polypeptide *per se*.

As conceded in the Action, Cozens *et al.* fail to teach or suggest recombinant expression of ANT polypeptides, much less the isolation of a recombinant ANT polypeptide, as presently claimed. Rather, Cozens *et al.* merely identified ANT-encoding nucleic acid sequences cloned into a non-expressing λ vector. Although Cozens *et al.* thus disclose *nucleic acid* sequences that can encode ANT polypeptides, these *nucleic acid sequences* clearly are <u>not</u> equivalent to an isolated ANT *polypeptide* according to the instant invention. Furthermore, Applicants submit that *E. coli* infected with a λ clone carrying an ANT nucleic acid sequence -- *i.e.*, a non-expressing clone-- cannot possibly be equivalent to an isolated recombinant ANT polypeptide according to the instant invention. In addition, Cozens *et al.* fail to disclose or in any way contemplate such a recombinant ANT polypeptide that is isolated from a host cell that lacks endogenous human ANT1 (SEQ ID NO:31) and ANT2 (SEQ ID NO:32) polypeptides, according to present claim 46.

Finally, Applicants submit that Cozens *et al.* fail to teach or suggest an *isolated* ANT3 polypeptide. As stated above, Cozens *et al.* merely describes the amino acid sequence of ANT polypeptides predicted to be encoded by ANT nucleic acid sequences. Cozens *et al.* absolutely fail to describe an *isolated* ANT polypeptide, as presently claimed. The Examiner appears to hold the position that a non-recombinant ANT polypeptide would anticipate the claimed recombinant ANT polypeptides. While Applicants disagree with this position, Applicants also submit that the Examiner's position is largely irrelevant to the current claims, which are drawn to *isolated* polypeptides, since nowhere do Cozens *et al.* teach or suggest an isolated polypeptide having at least 95% identity to ANT3. Applicants submit that nowhere in Cozens *et al.* is a polypeptide meeting all the elements of the presently claimed invention taught

or even suggested. The disclosure of Cozens *et al.* is at best limited to mere deduced sequence *information*, but no isolated polypeptide is disclosed by Cozens *et al.* Accordingly, Applicants respectfully submit that the present invention satisfies the requirements of 35 U.S.C. § 102(b) and, therefore, request that this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103(a)

In the Office Action, claims 42, 46-48 and 57 were rejected under 35 U.S.C. §103(a) as obvious over Cozens *et al.* (*J. Mol. Biol. 206*:261-280, 1989) in view of Adrian *et al.* (*Mol. Cell Biol. 6(2)*:626-634, 1986) and Rosenberg (*Protein Analysis and Purification: Benchtop Techniques*, Birkhauser, Boston, 335-347, 1996). In particular, it is asserted that it would have been obvious for a person having ordinary skill in the art to substitute the human ANT3 protein alleged to have been taught by Cozens *et al.* for the yeast ANT protein taught by Adrian *et al.* to obtain a fusion protein. In addition, the Action alleges that a person of ordinary skill in the art would have had a reasonable expectation of success because the preparation of a fusion protein and the incorporation of a protease cleavage site are standard methods in the art for the recombinant production and rapid purification of proteins, as demonstrated by Adrian *et al.* using ANT proteins.

Applicants respectfully traverse this ground of rejection and submit that Cozens *et al.*, Adrian *et al.*, and Rosenberg, taken alone or in combination, fail to teach or suggest the claimed invention. The present invention is directed, in pertinent part, to an isolated recombinant human adenine nucleotide translocator (ANT) polypeptide comprising an amino acid sequence that is at least 95 percent identical to a human ANT3 sequence as set forth in SEQ ID NO:33 and that is capable of binding an ANT ligand, or an isolated ANT fusion protein comprising such an ANT polypeptide fused to at least one additional polypeptide sequence. As set forth above, Cozens *et al.* concededly fail to teach or suggest a recombinant ANT polypeptide according to the instant invention. Further, the Patent Office also concedes that Cozens *et al.* fail to teach or suggest an isolated ANT fusion protein according to the instant invention. As discussed in greater detail below, Applicants submit that the deficiencies of Cozens *et al.* are not remedied by the disclosures of Adrian *et al.* and/or Rosenberg.

The disclosure of Adrian *et al.* is directed to a determination of whether the yeast ANT polypeptide contains mitochondrial targeting sequence motifs in common with other typical mitochondrial proteins, but Adrian *et al.* fail to contemplate in any way the recombinant expression of human ANT polypeptides or fusion proteins having at least 95% identity to human ANT3 and that are capable of binding to an ANT ligand, according to the present invention. Applicants respectfully submit that a careful review of Adrian *et al.* fails to reveal any evidence that the expressed yeast ANT fusion proteins described therein are capable of binding to an ANT ligand.

Furthermore, Applicants submit that the cited references, taken alone or in combination, fail to teach or suggest that recombinant ANT expression could be comparably achieved if human ANT sequences were substituted for the yeast sequences of Adrian *et al.* Applicants note that the Action fails to provide any evidence that the methods of Adrian *et al.* could be used to express and purify a presently claimed ANT polypeptide. Applicants note that the present claims are directed to polypeptides having at least 95% identity to full length human ANT3. Accordingly, the claimed polypeptides must be at least 95% the length of human ANT3, which is 299 amino acid residues in length. In contrast, the yeast ANT polypeptides expressed by Adrian *et al.* are truncated polypeptides that include less than 95% of the yeast ANT sequence. Indeed, as understood by the skilled artisan, the production of functional ANT polypeptides is by no means always a routine procedure (See, *e.g.,* the enclosed Declaration of Dr. Christen M. Andersen). Accordingly, Applicants submit that the skilled artisan would not have had a reasonable expectation of successfully producing the claimed human ANT3 polypeptides and fusion proteins, having at least 95% identity to full length human ANT3, based upon the expression of truncated yeast ANT fusion proteins in yeast cells, particularly absent any evidence that these fusion proteins would possess relevant biological activities, including those specifically recited in the instant claims.

Applicants also respectfully submit that the mere fact that the teachings of the cited references *can* be combined or modified, or that a person having ordinary skill in the art is *capable* of combining or modifying the teachings of the cited references, does not make the resultant combination *prima facie* obvious, as the cited documents must also suggest the desirability of the combination (*see, e.g., In re Mills*, 16 USPQ2d 1430, Fed. Cir. 1990; *In re*

Fritch, 23 USPQ2d 1780, Fed. Cir. 1992). Applicants submit that the cited documents absolutely do not teach or suggest the desirability of combining the references to achieve the presently claimed invention drawn to recombinant human ANT3 polypeptides, and, therefore, the Action fails to establish a *prima facie* case of obviousness.

Rosenberg is merely a general reference describing the construction and use of fusion proteins, including fusion proteins having an affinity tag and optionally a protease cleavage site to facilitate protein purification. Rosenberg fails, however, to provide any teaching or suggestion pertaining to the claimed isolated ANT polypeptides and ANT fusion polypeptides. The teaching of Rosenberg, therefore, is merely cumulative subject matter in view of the instant specification. Applicants note, for example, that the instant specification discloses several fusion enzymes and affinity tag sequences that are known in the art (*see, e.g.*, specification page 25, line 1 through page 26, line 27; Examples 1 and 2). Thus, the combined cited references do not render the claimed invention obvious. Rather, Applicants submit that the Action employs impermissible hindsight to allege that the combined references would have motivated an ordinarily skilled artisan to arrive at the present invention.

Hence, Applicants submit that the cited references alone or in combination fail to suggest that recombinant ANT expression could be achieved *with a reasonable expectation of success* if human ANT sequences were substituted for the yeast sequences of Adrian *et al.* In particular, the PTO fails to provide specific reasoning in support of the assertion that the present invention would have been obvious at the time of filing the instant application, given the level of ordinary skill in the art. By way of contrast, Applicants submit that if anything, the state of the art pointed away from arriving at the present invention with any reasonable expectation of success. To this point, Applicants have submitted herewith the Declaration of Dr. Christen Anderson, which describes the art-recognized difficulties and failure by others to express and isolate recombinant human ANT polypeptides.

For example, based on the teachings of Miroux *et al.* (1996 *J. Mol. Biol.* 260:289), a copy of which is enclosed for the Examiner's convenience, Applicants submit that a person having ordinary skill in the art would have understood that recombinant expression of an ANT polypeptide is hardly a routine matter. More specifically, Miroux *et al.* describe efforts to express various recombinant proteins, including mammalian ANT, in a bacterial expression

system. Multiple problems are described with regard to efforts to express recombinant ANT, including toxicity to host cells, poor solubility of the recombinant product and accumulation of recombinant ANT in inclusion bodies (*e.g.*, Miroux *et al.*, 1996 *J. Mol. Biol.* 260:289, at pages 290-291 and Table 1), which Applicants submit would be recognized by those familiar with the art as a form amenable neither to ready isolation nor to functional binding interactions with an ANT ligand.

Applicants, therefore, respectfully submit that it would be misguided to believe that the person having ordinary skill in the art at the time of the present application knew, with a reasonable expectation of success, how to arrive at the instant invention. Thus, where the art failed to suggest to the person having ordinary skill in the art that the presently claimed ANT polypeptides should be made according to the present invention, and where, for reasons discussed herein, such a skilled artisan would not have been provided with a reasonable expectation of success in doing so based on the cited documents, Applicants submit that *prima facie* obviousness has not been established. *See, e.g., In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants also respectfully submit that the present invention is non-obvious when "secondary" factors, and in particular the identification of a long-felt need and the failure of others, are considered. It is well established that considerations such as long-felt but unsolved needs, and the failure of others to arrive at applicants' invention, are not only relevant to the obviousness inquiry, but must be considered when present. *Custom Accessories Inc., v. Jeffrey-Allan Industries Inc.,* 807 F.2d 955; 1 USPQ2d 1196 (Fed. Cir. 1986); *Ryko Manufacturing Co. v. Nu-Star Inc.*, 950 F.2d 714, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991). As noted earlier, Applicants submit herewith the Declaration of Dr. Christen M. Anderson, which presents evidence of the importance of ANT polypeptides in human disease, the long-felt need for recombinant ANT polypeptides for additional research, and the unsuccessful attempts by other investigators to produce recombinant ANT polypeptides.

Hence, and as noted above, Applicants respectfully submit that where cDNA sequences encoding a human ANT polypeptide were known as early as 1987, and where recombinant protein expression methods were established well before 1987, a long-felt need for reliable expression of ANT polypeptides was present at the time of filing the instant application

in 1998. In addition, the attention directed to ANT polypeptides by numerous investigators, as evidenced by the references cited throughout the instant specification (*see, e.g.,* specification at page 18, lines 5-27; pages 44-45; Miroux *et al.*; and elsewhere) makes clear the desirability of being able to express recombinant human ANT that is capable of binding an ANT ligand. Moreover, and as stated above, Applicants are unaware of any successful production by others of an isolated recombinant human ANT polypeptide that is capable of binding an ANT ligand, or of isolated ANT fusion proteins, according to the instant invention. In view of the absence of any such disclosures from the art, and further in view of unsuccessful efforts to express recombinant ANT in a useful form (*e.g.,* Miroux et al., *supra*), Applicants therefore respectfully submit that the present invention is non-obvious when such secondary considerations are taken into account.

Applicants, therefore, respectfully submit that a *prima facie* case of obviousness has not been established by the Patent Office. Briefly, where claimed subject matter has been rejected as obvious in view of a combination of cited publications, a proper analysis under §103 requires, *inter alia*, consideration of three factors: (1) the combined references must teach or suggest all claim elements (*In re Royka*, 180 U.S.P.Q. 580, CCPA 1974); (2) the references must provide some teaching, suggestion, or motivation to combine or modify the teachings found therein to produce the claimed invention (*In re Vaeck*, 20 U.S.P.Q.2d 1438, Fed. Cir. 1991); and (3) the combined teachings of the references must indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success (*Id.*). In the instant case, the cited references meet none of these criteria. That is, as set forth above, the cited references taken alone or in combination would not have motivated a person having ordinary skill in the art to arrive at the instant invention with a reasonable expectation of success. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Additionally, applicants wish to call the Examiner's attention to several related co-pending applications having claims potentially directed to similar subject matter. Reference to the appended "Table of Co-Pending Applications" is therefore requested.

The Commissioner is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment to our Deposit Account No. 19-1090.

All of the claims pending in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. The Examiner is urged to contact the undersigned attorney if there are any questions prior to allowance of this matter.

Respectfully submitted,

Christen M. Anderson *et al.*

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Enclosure:
Miroux *et al.* (1996 *J. Mol. Biol.* 260:289)
14 Sheets of Replacement Drawings (Figures 1A-19)

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